

**REMARKS**

**Information Disclosure Statement**

Applicants have submitted a Supplemental Information Disclosure Statement containing copies of references, now labeled A05-A07, B10-B19 and C27-C79, listed on the attached revised form PTO-1449 entitled "List of References Cited by Applicant." Legible copies of references B10-B19 and C27-C79 are submitted herewith. Applicants respectfully request that the references be made of record in the application.

**Claims**

Upon entry of this amendment, claims 125-126, 128-129 and 131-140 are pending in the present application. Applicants have cancelled claims 100, 101, 103, 104, 109, 111-113, 117-124, 127 and 130 without prejudice to Applicants' right to pursue the subject matter of the cancelled claims in a related application. Claims 125 and 129 have been amended.

Claim 125 has been amended to clarify that the carrier is a bacterial toxin, for which support can be found in the instant specification, at, *e.g.*, page 27, line 34 through page 28, line 3. Claim 125 has also been amended to include the chemical linker characterized as CJ 11, for which support can be found in the instant specification, at, *e.g.*, page 36, line 9 of the instant specification. Q has been modified to be selected from the group consisting of: a protein or peptide carrier, a modified protein or peptide carrier, or another branch identified by its "CJ" reference number, for which support can be found in the instant specification, at, *e.g.*, on page 36, lines 15-34. Claim 129 has been amended to clarify that the carrier is bacterial toxin, pseudomonas exotoxin, for which support can be found in the instant specification, at, *e.g.*, page 28, lines 2-3. No new matter has been added.

## **I. Priority**

As amended, pending claims 125-126, 128-129 and 131-140 are entitled to priority to U.S. Application No. 08/720,487, filed September 30, 1996, now U.S. Patent No. 5,876,727. Support for linker group CJ 11 is described on page 36, line 9 of U.S. Application No. 08/720,487. Support for the Q group is found on page 36, lines 15-34 of U.S. Application No. 08/720,487. Support for the bacterial toxin carrier is found in U.S. Application No. 08/720,487 on page 27, line 34 through page 28, line 3, and specifically pseudomonas exotoxin is found on page 28, lines 2-3 of U.S. Application No. 08/720,487.

## **II. Response to Objections**

In response to the Examiner's rejection to the representation of CJ 10 in claim 125, the claim has been amended to recite the chemical structure of the CJ 10 linker group. Withdrawal of the objection is respectfully requested.

## **III. Rejection Under 35 U.S.C. § 112**

Claim 125 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In response to the rejection, Applicant has amended the language in claim 125 to "nicotine, a nicotine derivative or a salt thereof." The amendment clarifies that the claimed hapten encompasses nicotine itself as well as compounds that are derived from nicotine. Withdrawal of the rejection is respectfully requested.

**IV. The Claims Are Not Anticipated By U.S. Patent No. 5,164,504 to Walling *et al.***

Claims 100, 103, 111 and 125 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by U.S. Patent No. 5,164,504 to Walling *et al.* ("Walling"). The Examiner alleges that Walling discloses certain hapten-carrier conjugates wherein the hapten is cotinine, which is coupled to a protein carrier. For the reasons below, the rejection cannot stand and should be withdrawn.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Without conceding to the propriety of the rejection, and in order to expedite prosecution, Applicants have cancelled claims 100, 103, 111 and 127, and amended claim 125. Claim 125 has been amended to clarify that the carrier is a bacterial toxin. Walling does not describe a bacterial toxin carrier. Accordingly, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 102(b) is respectfully requested.

**V. The Claims are not Obvious in Light of Walling, Holmgren and Illum**

Claims 100-101, 103-104, 109, 111-113, 117, 120-132 and 136-140 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over Walling, Holmgren *et al.* *Am. J. Trop. Med. Hyg.* 50(5) suppl.: 42-54, 1994, "Holmgren," and International Patent Application, WO 94/27576 to Illum *et al.* ("Illum"). The Examiner alleges that it would have been obvious to modify the nicotine-derived carrier conjugate taught by Walling with the carrier taught by Holmgren, and the specific route of administration taught by Illum. Without conceding to the propriety of the rejection, and in order to expedite prosecution, Applicants have cancelled

claims 100-101, 103-104, 109 111-113, 117, 120-124, 127 and 130, and amended claims 125 and 129. For the reasons below, the rejection cannot stand and should be withdrawn.

“A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR v. Teleflex*, 550 U.S., 127 S. Ct. 1727 (2007).

As described above, Walling teaches the use of cotinine, a nicotine derivative, as a haptene coupled to a carrier. However, Walling does not teach the use of a bacterial toxin as a carrier. The Examiner attempts to overcome this omission by citing Holmgren. Holmgren teaches the use of cholera toxin B (CTB), a bacterial toxin, as an adjuvant for enteric vaccines. By reading Holmgren, one skilled in the art would in no way be motivated to combine the two references.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006); and MPEP § 2143.01.

Nowhere does Holmgren teach or even suggest using CTB as a carrier for small molecule haptens, such as nicotine or a nicotine derivative. Holmgren focuses on the potential use of CTB to specifically enhance mucosal immunity, in particular in connection with oral vaccines, to provide immunity against enterotoxins and viral infection. Holmgren is focused on the induction of a specific and local mucosal immune response to prevent enteric infection, such as a vaccine against diarrhea caused by enterotoxigenic *E.coli* producing CT-like enterotoxin(s). Holmgren even calls into question the ability of CTB to have an effective adjuvant effect in this specific anti-enteric context. There is nothing in Holmgren to suggest

that CTB could even be employed outside the context of an oral anti-enteric vaccine, let alone be used as a conjugate for a small molecule. Holmgren describes viral antigens, such as cholera, streptococcal protein antigen, Sendai virus, and peptide antigens derived from Herpes simplex virus (HSV)-2 glycoprotein D, for which a local mucosal immune response is required. Each of these antigens are capable of eliciting an immune response on their own. CTB is coupled to these antigens simply in order to enhance a mucosal immune response. On the contrary, nicotine having a molecular weight and steric size many magnitudes lower than that of the viral and bacterial antigens described in Holmgren, is incapable of eliciting an immune response on its own. Therefore, there would be no motivation for one skilled in the art to apply the teaching of Holmgren to nicotine.

Illum describes the administration of nicotine through a variety of routes, including parenteral. Illum describes the rapid absorption of the unconjugated small molecule nicotine. The delivery of nicotine itself is completely irrelevant to the present invention, i.e., nicotine conjugated to a large carrier such as a bacterial toxin. Most importantly for delivery, the polarity, molecular weight, steric bulk, and solubility are completely unrelated between free nicotine and nicotine bound to a bacterial toxin. There would be absolutely no expectation that the delivery method for one, would work for the other. Moreover, Illum in no way describes or suggests that the delivery methods presented would elicit an immune response for nicotine.

Considering that Walling does not describe a bacterial toxin carrier, Holmgren focuses on specific oral immune responses to bacterial and viral antigens that immunogenically are completely unlike small molecules, and Illum focuses on the delivery of free nicotine and does not relate to immune response, the references in combination do not teach, suggest, or motivate combination of the three prior art references to yield the nicotine-

carrier conjugates claimed in the present application. Accordingly, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) is respectfully requested.

## **VI. Double Patenting**

Claims 100-101, 103-104, 109, 111-113, 117-140 are rejected on the non-statutory ground of obviousness-type double patenting over claims 1-2, 4-5, 8-12 and 17-18 of U.S. Patent No. 5,876,727. Claims 125-126, 128-129 and 131-140 are pending in the current application. Applicants, upon indication of allowable subject matter, will submit a Terminal Disclaimer under 37 C.F.R. 1.321(c) of the above-identified application.

## **VII. Provisional Double Patenting**

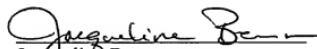
Claims 100-101, 103-104, 109, 111-113, 117-140 are provisionally rejected on the non-statutory ground of obviousness-type double patenting over claims 43-45, 47-50, 52-54, 56-65, and 74-82 of co-pending Application Nos. 11/066,718; 11/472,215; 11/472,216; 11/472,217; 11/472,218; 11/472,219; 11/472,220; 11/472,222; and 11/472,223. Claims 125-126, 128-129 and 131-140 are pending in the current application. Applicants, upon indication of allowable subject matter, will submit a Terminal Disclaimer under 37 C.F.R. 1.321(c) of the above-identified application.

**CONCLUSION**

Applicants respectfully request that the Examiner consider the amendments and the remarks made herein, and that the Examiner enter them into the record for the present application. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to contact the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

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